30

Date 4-2-1951

Attachment 1.

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. Md. R. Islam

Application No. 81-005

Title of Study Use of Base-Precursors as a substitute of Bi-carbonate in the oral rehydration solution.

Trainee Investigator (if any) Dr. Masud Ahmed

Supporting Agency (if Non-ICDDR,B) Nil

Project status:
(✓) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects (Yes) No
   (b) Non-ill subjects Yes (No)
   (c) Minors or persons under guardianship (Yes) No
2. Does the study involve:
   (a) Physical risks to the subjects (Yes) No
   (b) Social Risks Yes (No)
   (c) Psychological risks to subjects Yes (No)
   (d) Discomfort to subjects (Yes) No
   (e) Invasion of privacy Yes (No)
   (f) Disclosure of information damaging to subject or others Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) Yes (No)
   (b) Use of fetal tissue or abortus Yes (No)
   (c) Use of organs or body fluids (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study (Yes) No
   (b) Procedures to be followed including alternatives used (Yes) No
   (c) Physical risks (Yes) No
   (d) Sensitive questions Yes (No)
   (e) Benefits to be derived (Yes) No
   (f) Right to refuse to participate or to withdraw from study (Yes) No
   (g) Confidential handling of data (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure (Yes) No
5. Will signed consent form be required:
   (a) From subjects (Yes) No
   (b) From parent or guardian (if subjects are minors) (Yes) No
6. Will precautions be taken to protect anonymity of subjects (Yes) No
7. Check documents being submitted herewith to Committee:
   ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   ✓ Informed consent form for subjects
   ✓ Informed consent form for parent or guardian
   ✓ Procedure for maintaining confidentiality
   ___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
   1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
   2. Examples of the type of specific questions to be asked in the sensitive areas.
   3. An indication as to when the questionnaire will be presented to the Cttee. for review.

We agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

R. Islam.
Principal Investigator

Trainee

81-033

rec'd 6/2/81

SECTION I - RESEARCH PROTOCOL

1. TITLE: USE OF BASE-PRECURSORS AS A SUBSTITUTE OF BI-CARBONATE IN THE ORAL REHYDRATION SOLUTION.

2. PRINCIPAL INVESTIGATOR: DR. MD. RAFIQUL ISLAM

   CO-INVESTIGATORS: DR. P.K. BARDHAN, DR. MASUD AHMED, DR. A.R. SAMADI, MR. AKBAR ALI

3. STARTING DATE: February, 1981

4. COMPLETION DATE: July, 1981

5. TOTAL COST: $ 18,324

6. SCIENTIFIC PROGRAMME HEAD:

   This protocol has been approved by the Pathogenesis & Therapy Working Group.

   Signature of Scientific Programme Head: _____

   Date: 4/2/81

7. ABSTRACT SUMMARY:

A clinical trial is propsosed to define the usefulness of base precursors like sodium acetate & sodium citrate as a substitute of sodium bicarbonate in the oral rehydration solution for the treatment of cholera and non cholera diarrhoea in adults and children. This study is planned to comprise 100 patients 2-10 yrs and 100 >10 years of age with acute watery diarrhoea and with moderate dehydration by

clinical judgment. All patients will be put on oral rehydration therapy. Only dark field positive cases with V. cholera will be treated with Tetracycline. 50 cases in each group (25 adult & 25 children) will be treated with one of the four oral solutions containing, bicarbonate, acetate, citrate or without base in a randomised way. These four groups will be compared subsequently to determine (a) whether other base precursors can correct metabolic acidosis resulting from continued base loss due to acute diarrhoea, (b) whether ORS without any base can maintain electrolyte balance, particularly serum bicarbonate.

8. REVIEWS:

(a) Research involving human subjects: _____

(b) Research Committee: _____

(c) Director: _____

(d) BMRC: _____

(e) Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective:

The objective of this study is to define whether (a) base precursors like acetate, citrate can be used as a substitute of bicarbonate in the oral rehydration solution for correction of metabolic acidosis resulting from acute watery diarrhoea. (b) ORS without any base can maintain electrolyte balance particularly serum bicarbonate.

2. Background:

In acute watery diarrhoea, there are losses of water as well as electrolytes like Na, K, Cl & bicarbonate in the stool[1]. Proper replacement of water & electrolytes is the principal rationale behind the formulation of various intravenous and oral rehydration solution used in the management of acute diarrhoeal disease.

Various intravenous solutions like Dacca solutions (5:4:1), acetate solution, Ringer lactate, saline-lactate (2:1 ratio) etc.were found to be quite effective for correction of electrolyte imbalance including acidosis. Bicarbonate immediately can correct acidosis whereas other base-precursors like acetate, citrate, lactate have to be converted to bicarbonate through tricarboxylic acid cycle of Krebs in the liver.

The possibility of treating cholera patients with an oral solution was indicated by balance studies of cholera patients in 1962. These studies[2,11] showed that cholera patients could absorb water, potassium and bicarbonate but not sodium and chloride, when solutions of varying concentrations were given by month. It was further shown that when d-glucose was added to oral solutions, glucose as well as sodium and chloride ions were absorbed[2,3]. This was the basis for the evolution of oral therapy initially with glucose & later on with sucrose - electrolyte solution.

The current ORS as recommended by WHO contains Na^+ - 90, K^+ - 20, Cl^- - 80 & $Hco3^-$ - 30 mmols/L and 20 gm/L (111 mmols/L) glucose and is being widely used all over the world for the treatment of diarrhoeal diseases. Recent studies have shown that glucose can be substituted with sucrose (40gm/L)[9,10]. Sodium bicarbonate is currently being used in the ORS for the correction of acidosis due to diarrhoea. Bicarbonate also enhances absorption of sodium. Its omission eliminates the bicarbonate-linked sodium absorption, and delays or in severe cases makes impossible the correction of acidosis, thus possibly augmenting the risk of hyperkalaemia associated with acidosis. Islam et al published a paper in which mild to moderately severe adult non-cholera diarrhoea cases were treated with oral rehydration fluid lacking bicarbonate and adequate potassium. The serum bicarbonate and potassium remained low for a long period of time inspite of optimal hydration [12]. Similar observations have been found in children also.

Bicarbonate is generally cheap and widely available. A concentration of 30 mmols/L appears to be sufficiently effective and safe. But there are certain disadvantages of bicarbonate. 1) Since this is an alkali & directly absorbed from gut, it may produce metabolic alkalosis resulting tetany & hypocalcemia. We have observed several cases of heavily purging cholera who developed severe carpopedal spasm secondary to alkalsis both from intravenous or oral rehydration solutions containing bicarbonate. 2) Bi-carbonate has short shelf life. 3) Bacteria can easily multiply in this alkaline medium.

For clinical management of Acute diarrhoea, WHO organised a Scientific Working Group meeting at New Delhi in 1978 with an international group of experts who recommended for clinical trial of other base-precursors as a substitute of bicarbonate. The group thought that as acetate should have a better shelf-life than bicarbonate and is relatively inexpensive, studies should be done to determine whether acetate is absorbed during diarrhoea and can be substituted for bicarbonate in the formulation. A comparative clinical trial with acetate vs. bicarbonate has been underway at Calcutta. The preliminary report as presented in the last meeting of the Indian Society of Gastroenterology indicated promising and encouraging result with acetate as a substitute of bicarbonate in the ORS. Further observations are necessary before its practical use.

On the other hand sodium citrate had been used along with bicarbonate in different concentrations with fair success[4,6,8,..]. A comparative limited study using 30 mmols/L of citrate with that of bicarbonate (Citrate - 13 cases, bicarbonate - 9 cases) was done in ICDDR,B[13] (unpublished data) which had shown that citrate is equally effective as bicarbonate in the correction of acedosis. The effect was observed as early as 4 hours after institution of oral therapy. Citrated oral rehydration solution was found to be more palatable and acceptable to both adult & children patients. There was observed some positive trend in oral therapy success rate in citrate group than bicarbonate goup (9/15 vs. 5/9)[13].

Seriki in 1978 had used 1/6 M lactate along with saline & glucose as an oral rehydration solution for the management of dehydration by continuous intragastric infusion with promising result. S. Dey & Naik have also used lactate along with bicarbonate and citrate[4,7...] in ORS without any danger.

3. Rationale:

Base precursors like acetate, citrate are stable salts. Sodium acetate is easily available & cheap in comparison to sodium bicarbonate. Since bicarbonate is directly absorbed from the gut it may cause alkalosis in some cases, whereas other base precursors have to be converted to bicarbonate in the liver. So there is less chance of the patient to become alkalotic. Oral therapy packets containing base precursors are

presumed to have better shelf life & more palatable and thereby acceptable to both adult & children. This will help us in minimizing oral therapy failure rate.

B. SPECIFIC AIMS

1. To see whether base precursors like acetate, citrate are absorbed from the gut & can substitute bicarbonate for the correction of acidosis.

2. To compare the effectiveness of oral solution without containing any base (bicarbonate, acitate or citrate).

METHODS AND PROCEDURE

1. Subjects: 200 patients, >2 yrs of age, weighing more than 10 kg on admission with history of acute watery diarrhoea of less than 24 hours duration and judged clinically moderately dehydrated & who will still be able to drink oral fluid will be selected for the study. The patients will be stratified according to age with 100 pts >10 yrs and 100 < 10 years. Patients will be excluded from the study if they have received anitbiotics within a week prior to hospitalization, have complications or are severely malnourished. The patient will be selected each morning with the first 2 children 10 and the first 2 adults 10 years, fulfilling the above criteria will be requested to participate in the study.

Eligible patients (or their parents in case of children) will be informed of the study and if they agree to participate they will be included in the study.

2. Clinical Procedures: selected patients will be admitted directly in the study ward & the following procedures will be followed, on admission

a) body weight.

b) History and thorough physical examinations vital signs recording.

c) venous blood for haematocrit, serum sp. gravity, electrolytes, urea & creatinine.

d) catheter specimen of stool will be sent for microscopic examination, Dark field exam & culture in all plates for cholera, salmonella, shigella & E. coli ST + LT. Stool also be saved for rotavirus detection by ELISA technique.

No intravenous fluid will be administered. Initial rehydration as well as subsequent maintenance of hydration status will be scheduled to be done with any one of the four groups on trial on strict randomized basis.

Only dark field positive cases for V. cholerae will be treated with Tetracycline (250 mgm every 6 hourly for children and 500 mgm every 6 hourly for adults above 10 yrs for 2 days only).

All 4 groups of ORS will be made equally attractive with orange flavour & same type of colouring agent. Patient will be given oral fluid ad lib to drink as long as diarrhoea persists. Free water will not be restricted. Also there will be no dietary restrictions.

Clinical evaluation of hydration status, acidosis, vital signs, intake (ORS & water) and output measurement of stool, urine and vomitus will be recorded at 4 hours after admission and every 8 hours thereafter. A body weight and Sp. gravity will be determined 12 hours after admission.

A summary of clinical measurements is as follows:

	Adm.	4 hrs.	12 hrs.	20 hrs.	28hrs.	52 hrs.
Cl. evaluation	X	X	X	X	X	X
Hct	X	X	-	-	X	X
Sp. Gr.	X	X	-	-	X	X
Serum Electro-lytes, urea, creatinin	X	X	-	-	X	X
Weight	X	X	X		X	X
Intake	X	X	X	X	X	X
Output	X	X	X	X	X	X

The clinical evaluation will include examinations for skin turgor, mucous membrane, eye sign, pulse volume, B.P., and signs of pulmonary edema etc. Patients will be under constant observations in the study ward. Special attentions will be given for the appearance of any basal crepitation as a complications of pulmonary edema. Such cases will be excluded from study.

D. SIGNIFICANCE

From the result of this study, it should be possible to determine the comparative safety and efficacy of these four types of oral solutions in the treatment of watery diarrhoea of any etiology.

E. FACILITIES REQUIRED

i) Office for investigator in study ward is already available.

ii) Laboratory facilities for routine microbiology, Biochemistry, Clinical Pathology will be utilized.

iii) Hospital Resources - The study ward will be used and on average four patients are needed per day thus a total of 12 beds (6 adults & 6 children) will be sufficient.

iv) Animal Resources: For E. coli study.

F. COLLABORATIVE ARRANGEMENT - Nil.

Failure of the therapy will be defined as the inability to re-hydrate or maintain hydration or failure to maintain electrolyte balance. Failure of initial hydration or to maintain hydration based on clinical and laboratory signs e.g. fall in body weight, poor skin turgor, weak pulse, fall in B.P. and rise in plasma Sp. Gravity more than 1030 & development of signs and symptoms of electrolyte imbalance including pulmonary edema during therapy will be considered as a treatment failure. Failure cases will be treated with appropriate intravenous solutions.

3. Randomization

Patients will be randomized to one of the four group by choosing a slip of paper from an envelope. This paper will contain one of 8 letters (A,B,C,D,E,F,G,H). 2 of these will contain one of the four ingredients under trial. 8 instead of 4 will be used to protect the possible biasness of the study.

Patient will be discharged when they pass soft stool or have had two consecutive 8 hour periods with less than 5 ml/kg/8hrs. period of liquid or water stool.

4. Analysis of data:

After the study is completed, it should be possible to evaluate statistically the success of these oral fluids after analysing:

(i) Failure as defined above.

(ii) Duration of diarrhoea.

(iii) Volume of diarrhoea stool.

(iv) Amount of oral fluid taken.

(v) Any complication during therapy.

COMPOSITION OF ORAL FLUIDS TO BE USED (Grams/L)

	Nacl	Kcl	$NaHco_3$	Na-acetate	Na-citrate	Sucrose
1. ORS with Bicarbonate	3.5	1.5	2.5	-	-	40
2. ORS with Acetate	3.5	1.5	-	4.1	-	40
3. ORS with Citrate	3.5	1.5	-	-	2.58	40
4. ORS without base	5.2	1.5	-	-	-	40

(Each type of fluid will provide Na-90, K-20, Cl-80, Sucrose - 111 (Glucose)/L & base 30 mmols/L except 4th group (ORS without base) which contains a bit high chloride - 110 mmols/L but no base).

References

1. Phillips, R.A., Water and Electrolyte losses in Cholera. Fed. Proc. 23:705, 1964.

2. Hirschhorn N, et al: Decrease in net stool output in cholera during intestinal perfusion with glucose containing solutions. New Eng. J. Med. 279:176, 1968.

3. Nalin, D.R., Cash, R.A., Islam, M.R., et al: Oral Maintenance Therapy for Cholera in Adults. Lancet 2:370, 1968.

4. DeS, Oral Glucose - Electrolyte Solution in the Treatment of Cholera and other diarrhoeas. J. Ind. Med. Assoc. 65:230-232, 1975.

5. Seriki, O., Management of Moderately Severe Dehydration by continuous intragastric infusion of electrolyte solution. Trop Doctor 8:134-136, 1978.

6. Nalin, D.R. et al: The optimal Oral Therapy formula for Cholera-like diarrhoeas: Proc. of the Sixth Annual International Epidemiologic Association Scientific Meeting Belgrade, Savremena Administracya, pp 1048-1057, 1971.

7. Naik, N.V. et al. Oral rehydration in acute Gastroenteritis in Young Children., Ind. Pediatrics 13:127-133, 1976.

8. Rahilly P.M. et al: Clinical Comparison between Glucose and Sucrose additions to a basic Electrolyte mixture in the outpatient management of acute Gastroenteritis in children.

9. Palmar D.L. et al. Comparison of Sucrose and Glucose in the Oral Electrolyte Therapy of Cholera and other severe diarrhoeas. N. Eng. J. Med. 297, 1107-1110, 1977.

10. Sack D.A. et al: Oral hydration in Rotavirus diarrhoea. A double blind comparison of Sucrose with Glucose - electrolyte solution. Lancet, Aug. 5, 1978.

11. Love A.H.G.: Proceedings of Cholera Research Symposium 1965. Honolulu, Washington, D.C.

12. Labun-Gur (Common Salt & Brown Sugar) Oral rehydration solution in the diarrhoea of adults. J. of Tr. Med & Hygeine.

13. Unpublished data: Akbar Ali, ICDDR,B

SECTION III - BUDGET

DETAILED BUDGET

1. Personnel Services

Name	Position	% of effort	Project Requirement Taka	Dollar
Dr. M.R. Islam	Principal Investigator	25%	13000	
Dr. P.K. Bardhan	Co-Investigator	25%	5000	
Dr. Masud Ahmed	Clinical Research Fellow	50%	9000	
Dr. A.R. Samadi	Head, Dacca Station	5%	-	750
Mr. Akbar Ali	Head, Bio-Chemistry	10%	3000	
3 Senior Staff Nurse		25%	6894	
1 Study Clerk		25%	1932	
Bacteriology Technician		1 person month	3000	
Clinical Path. Tech.		1 person month	3000	
Veterinarian			2000	
			49826	750

2. Supplies & Materials:

Stool culture exam 200 specimens	5000	-
Stool microscopic exam 200 specimens	1500	-
Hct & Sp. Gravity exam 800 specimens	1600	-
Electrolytes, urea & creatinin exam 800 specimens	2400	-
Adrenal cell assay 1000 isolates	2000	-
Infant mouse assay 400 isolates	4000	-
ELISA test - 200 specimen	600	-
Glass ware, plastic	-	250

			Taka	Dollar
Bicarbonate containing ORS				
Acetate	"	" 20 litres on average	4000	-
Citrate	"	" per patient		
No base	"	" Taka 1 per litre (Approx)		
			21100	250

3. Equipment - Nil.

4. Hospitalization - 200 patients x 2½ days/pt 75000 -

5. Out patient - Nil.

6. Transport - Nil.

7. Travel (International) - 3000

8. Transport of Things - Nil.

9. Rent - Nil.

10. Printing : Forms 1000 -
Publication - 300

11. Contractual Service - Nil.

12. Construction - Nil.

SECTION III - BUDGET

BUDGET SUMMARY	Taka	Dollar
1. Personnel	49,826	750
2. Supplies	21,100	250
3. Equipment	-	-
4. Hospitalization	75,000	-
5. Outpatient	-	-
6. Transport	-	-
7. Travel	-	-
8. Transport of Things	-	-
9. Rent	-	-
10. Printing	1,000	300
11. Contractual Services	-	-
12. Construction	-	-
Total	146,926	4,300
30% overhead	44,078	1,290
	191,004	5,590

Convertion rate $ 1=Tk. 15, $12,734

Grand Total $ 18,324

ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

A clinical trial is proposed on 200 patients to define the usefulness of sodium acetate and sodium citrate as a substitute of sodium bicarbonate in the oral rehydration solution and also compare the effectiveness of these solutions with a controll group receiving ORS without any base for the treatment of acute watery diarrhoea. 100 children (2-10 yrs) and 100 adults who report to the outpatient centre with moderate dehydration on clinical examination & still will be able to drink oral fluid will be selected for the study. No intravenous gluid will be used & initial hydration and subsequent maintenance therapy will be done by oral therapy alone. 50 Pts in each group (25 adults 10 yrs and 25 children 10 yrs) will be treated with one of the four oral solutions.

Regular clinical evaluation to detect any untoward symptoms like palmonary edema etc during treatment period will strictly be observed at regular interval of every 4 hours. Only 2-3 ml of venous blood will be drawn each time at 0,4,28 & 48 hours of admission for Hct, Sp. gravity, serum electrolyte, urea & creatinin estimations. Body weight, intake & output record will be maintained at 0,4,12,20, 28 & 52 hrs of hospitalization.

Only dark-field positive cases with V. cholera will be treated with tetracycline.

Patients will be given oral fluid and like to drink as long as diarrhoea persists. Free water & diet will not be restricted during the study.

Failure of the therapy will be defined as the inability to rehydrate or maintain hydration status based on clinical evaluation (fall in body wt, weak or absent radial pulse, persistent vomiting, restlessness or development of palmonary edema etc) and laboratory findings as rise in serum specific gravity > 1030, development of serious electrolyte imbalance like severe acedosis (Co_2 < 15 mmols/L) etc. These oral therapy failure cases will be treated with an appropriate solution intravenously. Appropriate antibiotics and medical care will be given if any bacterial complication developed during treatment.

There are no potential risks involved in the study.

Consent form is attached.

Patients will be potentially benefitted from this study. We anticipate that sodium citrate and sodium lactate will be equally effective as sodium bicarbonate in the oral rehydration therapy. Kidney will be able to regulate serum bicarbonate level in those who will not receive any base in their oral therapy.

Only 4 blood samples will be needed for the study.

CONSENT FORM

(STATEMENT READ AND EXPLAINED VERY CLEARLY
TO THE SUBJECT WHEN CONSENT IS OBTAINED)

The ICDDR,B is carrying out research to develop most economic but effective way to treat diarrhoea in a very simple way like oral rehydration therapy. We will be trying 4 kinds of oral solutions to treat diarrhoea. They were found reasonably effective in previous studies without any serious complications. We want to compare the relative effectiveness of these four types of oral rehydration solutions to know the best type for the treatment of acute watery diarrhoea. We like you to participate in the study for the well being of mankind.

If you decided to participate in our study, you can expect that

1. You will be given best possible care for your diarrhoea.
2. You will be needed to stay at least 2-3 days or even more until your diarrhoea slops.
3. While you are in hospital, we want to test total of 4 samples of blood (about 2-3 cc. each time) to know your health position.

These are all routine tests.

4. If the oral solution given to you fails to treat you by any chance or cause any sort of unbearable discomfort, you will be taken off from the study and will be treated with proper intravenous fluid.

5. If you do not like to participate in the study, still you will be treated like others in this hospital.

6. Besides, if you wish you are at liberty to withdraw from the study at any time without any obligations and jeopardizing your medical care and treatment.

understanding and realizing fully if you are willing voluntarily to participate in the study, then please sign your name or give left thumb impression below.

Signature : _____

or Left thumb impression of the patient or legal guardian in case of child.

_____
Signature of Investigator

Date: _____

Date .....

ICDDR,B Admission No. .....